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EDITORIAL COMMENTARY

A Proposed Etiology for an Aberrant Response to Enteric Adenovirus Infection in Previously SARS-CoV-2-Infected Children With Acute Hepatitis

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As of May 3, 2022, 163 cases of acute hepatitis of unknown etiology have been reported in children in the United Kingdom, and as of May 1, 2022, approximately 81 additional cases have been reported from the European Union (EU) and European Economic Area (EEA) (n = 36), the United States (n = 31), Israel (n = 12), Singapore (n = 1), and Japan (n = 1) with ongoing surveillance [1–3]. The World Health Organization (WHO) defines a probable case as a person presenting with an acute hepatitis (with hepatitis serologies negative for acute hepatitis A-E) with serum transaminase >500 IU/L (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]), who is 16 years and younger, since October 1, 2021. In addition, an epi-linked case is defined as a person presenting with an acute hepatitis (non–hep A-E) of any age who is a close contact of a probable case, since October 1, 2021 [4].

Retrospective investigation of the probable cases in the United Kingdom failed to identify a common environmental exposure (ie, food and toxins) [1]. Detailed laboratory investigation revealed that adenovirus was the most common pathogen identified in 91 out of 126 cases (72%), with type 41F detected in all subtyped adenovirus isolates detected from blood (18 out of 91) [1]. Since the end of 2021, an exceedance in adenovirus has been reported in children less than 9 years old from fecal and respiratory samples [1]. A similar trend has not been documented for older children or adults (these data were based on laboratory reports from the Second Generation Surveillance System [SGSS] where typically the detection of adenovirus is performed through amplification of a highly conserved target) [1]. Among the WHO-defined probable cases tested at hospital admission or attendance, 18% (24 out of 132) were positive for SARS-CoV-2. In addition, retrospective serology for SARS-CoV-2 antibodies is being conducted [1]. The corresponding positivity rate for SARS-CoV-2 in children aged 2-6 and 7-11 years during March and April 2022 in the United Kingdom is approximately 5%-8% and 3%-5%, respectively [1]. Moreover, the cumulative SARS-CoV-2 seropositivity rates during January and February 2022 in the United Kingdom were estimated to be approximately 47% and 67% in children aged 1-4 and 5-11 years, respectively [1]. Other viruses were detected in the blood of children who met the WHO case definition for probable acute hepatitis, including Epstein-Barr virus (EBV), enterovirus, cytomegalovirus, human herpes virus 6 (HHV-6), and HHV-7, but adenovirus was more frequently detected among the cases (detailed data were not available from the epidemiological report) [1]. Notably, no epidemiological linkage was reported among the children with acute hepatitis cases in England [1]. Laboratory investigation of 9 cases of severe acute hepatitis in the United States revealed similar findings with 9 (100%) with adenovirus detected via polymerase chain reaction (PCR) from whole blood [5]. All 9 patients tested positive for adenovirus, and 6 tested positive for EBV with serology suggestive of low-level EBV reactivation [5]. Laboratory tests identified that some of these children had adenovirus type 41, which more commonly causes pediatric acute gastroenteritis [5]. Additionally, some showed a history of other viruses including enterovirus/rhinovirus, metapneumovirus, respiratory syntactical virus, and human coronavirus OC43. Furthermore, other US cases have not been linked to a preceding adenovirus infection, when adenovirus has been assessed [5]. Interestingly, none of the 9 children had documented history of previous SARS-CoV-2 infection, and none of the children had positive nucleic acid amplification tests for SARS-CoV-2 [5].

Moreover, there is no evidence for an association of acute hepatitis with

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SARS-CoV-2 vaccination because the majority of children with acute hepatitis were unvaccinated; 75% of probable cases were unvaccinated with COVID-19 vaccination in less than 5 age-eligible children with acute hepatis [1].

A plausible hypothesis for the etiology of severe acute non–A-E hepatitis in children is infection with enteric adenovirus strain (F type 41) [1, 6]. Reports including the largest cohort from the United Kingdom [1] noted a high correlation ($R2 = 0.85$; $P < .001$) between adenovirus detection and cases of acute hepatitis over the first 13 weeks of 2022.

Enteric adenoviruses (usually F type 40/41) have been associated with gastroenteritis of variable severity although preceding infection has not previously been linked to severe acute hepatitis in immunocompetent children [7]. Therefore, it is possible that there are other exposures in addition to adenovirus infection that could account for acute hepatitis in children.

Linking the international clustering of acute pediatric hepatitis cases to a previous SARS-CoV-2 infection is based on an increase in SARS-CoV-2 seropositivity documented in the United States and the United Kingdom [1]. Assuming that reporting reflects population prevalence, and also children prevalence, the notable rates of SARS-CoV-2 in Europe, Israel, and the United States parallel the spatial distribution of cases of acute hepatitis of unknown etiology and deaths attributed to SARS-CoV-2 from these locations [8]. From December 1, 2021, until the end of April 2022, the cumulative SARS-CoV-2 cases per million in the total population were much higher in Europe (257 043) and North America (161 389) compared with Asia (31 796), and a similar trend was reported for COVID-19 deaths in the total population with the cumulative numbers being 2 426, 2 398, and 305 per million, respectively [8].

Due to SARS-CoV-2-related mitigation measures, children, especially those of younger ages, had less exposure to respiratory and enteric viruses. Once mitigation measures were removed and respiratory and enteric viruses began recirculating, some previously immune-naïve children may have mounted aberrant immune responses to infections with these viruses. Previous exposure to SARS-CoV-2 may have also primed some children to have an aberrant response to a circulating adenovirus or other viral infection.

The potential mechanism of acute hepatitis might be related to immune activation due to viral persistence and release of SARS-CoV-2 proteins in the intestinal epithelium [9]. Repeated immune activation might be mediated by a superantigen motif within the SARS-CoV-2 spike protein. Immune cell activation has been proposed as a potential cause of multisystem inflammatory syndrome in children [9].

The low detection of SARS-CoV-2 antibodies from children with severe acute hepatitis may not fully reflect previous SARS-CoV-2 exposure, although no other parameter can be used to detect the past SARS-CoV-2 infection.

Alternative etiologies of the current severe acute hepatitis in children might be: (1) a new adenovirus variant, (2) another so far unidentified novel pathogen, or (3) exposure to a toxin or an environmental factor. However, the absence of epidemiological linkage of hepatitis cases makes the hypothesis of a new adenovirus variant or a new pathogen less likely. If the cases of acute hepatitis were attributed to a transmissible novel adenovirus strain or new pathogen, it is likely that the cases would be clustered and cases might be seen in close contacts. In the case of a less transmissible adenovirus strain or new pathogen, cases could not be epidemiologically linked, but then we might expect less geographical distribution. Similarly, although previous exposure to a toxin or an environmental factor cannot be excluded, this hypothesis is less plausible due to the extensive geographic dispersal of the acute hepatitis cases.

Although there may be several etiologies for these presentations, we feel that an enteric adenovirus infection in a setting of high prevalence of previous SARS-CoV-2 circulation provides the most likely explanation for the current severe acute non–A-E hepatitis in children. Our hypothesis is based on the information to date that is known data about the current acute hepatitis [1–5], laboratory investigation [1, 5] as well as the geographic distribution and dispersal, the timeline of presentation, the correlation between the acute hepatitis and adenovirus positive cases, and findings of the absence of epidemiological linkage among cases. Although these cases are rare, an adenovirus infection in a previously SARS-CoV-2-infected host with a naive immune system may be a plausible explanation for an aberrant response resulting in severe acute hepatitis in children.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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